

[received by the International Bureau on 10 December 1999 (10.12.99);  
original claims 1, 6, 11, 12, 18, 25, 30, 53, 54 and 59 amended;  
remaining claims unchanged (12 pages)]

1. A formulation comprising a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, with a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.
2. A formulation of Claim 1, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.
3. A formulation of Claim 2, wherein the concentration of FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.
4. A formulation of Claim 3, further comprising an isotonicity agent.
5. A formulation of Claim 4, further comprising a physiologically acceptable buffer.
6. A formulation comprising a non-gaseous preparation of FSH or a FSH variant lyophilized in a first vial, and a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.
7. A formulation of Claim 1, wherein said FSH or a FSH variant and preservative are in solution.
8. A formulation of Claim 1, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:
- (a): α-subunit: (SEO ID NO:1)

- FPDGEFTMQGCEPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMVLVPMK  
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHHKS  
β-subunit: (SEQ ID NO:2)  
RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL  
5 VYETVKVPGCAHHADSLYTPVATECHCCKDSDSTDCTVRGLGPSYCSFRIKE  
(b): α-subunit: (SEQ ID NO:3)  
FPDGEFTMQDCEPECKLRENKYFFKLGVPYQCKGCCFSRAYPTPARSKKTMVLVPMK  
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI  
β-subunit: (SEQ ID NO:4)  
10 NSCELTNITIAVEKEEGCFICITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
VYETVKVPGCAHHADSLYTPVATACHGKCNDSSTDCTVRGLGPSYCSFGDMKE  
(c): α-subunit: (SEQ ID NO:5)  
APDVQDCEPCTLQENPFPSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHHKS  
15 β-subunit: (SEQ ID NO:6)  
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
VYETVRVPGCAHHADSLYTPVATQCHGKCDSDSTDCTVRGLGPSYCSFGEMKE  
(d): α-subunit: (SEQ ID NO:7)  
FPDGEFTMQGCEPECKLKENKYFSKLGAPYQCMGCCFSRAYPTPARSKKTMVLVPMK  
20 ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHHKS  
β-subunit: (SEQ ID NO:8)  
NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
VYETVKVPGCAHHADSLYTPVATECHGKCDSDSTDCTVRGLGPSYCSFSEMKE  
(e): α-subunit: (SEQ ID NO:9)  
25 FPDGEFTMQGCEPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMVLVPMK  
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHHKS  
β-subunit: (SEQ ID NO:10)  
RSCELTNITITVEKEECFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL  
VYETVKVPGCAHHADSLYTPVATECHGKCDSDSTDCTVRGLGPSYCSFSDIRE  
30 (f): α-subunit: (SEQ ID NO:5)  
APDVQDCEPCTLQENPFPSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHHKS  
β-subunit: (SEQ ID NO:11)  
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
35 VYETVRVPGCAHHADSLYTPVATQCHGKCDSDSTDCTVRGLGPSYCSFGE

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

5 NSCELTNITIAIEKEEERCFISINTTWCAGYCYTRDLVYKDPARPKIQTCTFKE  
VYETVRVPGCAHHADSLYTPVATOCCHCGKCDSDSTDCTVRGLGPSYCSFGEM

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQTCTFKEL  
VYETVRVPGCAHHADSLYTPVATOCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

15 comprises administering to a patient in need thereof a  
formulation according to Claim 1.

patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

solution formulation of a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, which comprises admixing said FSH or a FSH variant and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, 25 alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof, in an aqueous diluent.

pharmaceutical use, comprising packaging material and a vial comprising a solution of a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, and a preservative solution, wherein said packaging material

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comprises a label which indicates that said solution may be held over a period of 24 hours or greater.

13. The article of manufacture of Claim 12,  
wherein said vial is a glass container having a stopper for  
5 multi-use administration.

14. The article of manufacture of Claim 12, wherein said vial is a blister pack, capable of being punctured and used in pulmonary administration.

15. The article of manufacture of Claim 12,  
10 wherein said vial is a pen-injector device.

16. An article of manufacture, comprising packaging material, a first vial comprising lyophilized FSH or a FSH variant, containing an alpha and beta subunit, and a second vial comprising a preservative solution, wherein said packaging material comprises a label which instructs a patient to reconstitute the said lyophilized FSH or a FSH variant in the preservative solution for use over a period of 24 hours or greater.

17. The article of manufacture of Claim 16,  
20 wherein said first vial and said second vial are embodied in  
a pen-injector device.

18. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a preserved solution of a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, said solution being suitable for administration over a period of 24 hours or greater.

19. A method of using a stable solution of FSH or a FSH variant, containing an alpha and beta subunit to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of FSH or a FSH variant in a stable solution, said solution being suitable for administration over a period of 24 hours or greater.

35                    20.            The use of at least one alpha or beta  
polypeptide of a FSH or a FSH variant in the preparation of

a preserved formulation adapted for administration over a period of 24 hours or greater.

21. A stable formulation comprising at least one FSH or a FSH variant, containing an alpha and beta subunit, and phosphate buffer containing saline or a salt, wherein said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

22. A formulation of Claim 21, wherein the concentration of said FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

23. A formulation of Claim 21, further comprising an isotonicity agent.

24. A formulation of Claim 21, wherein said buffer is phosphate buffered saline.

25. A formulation comprising a first vial containing a nongaseous preparation of FSH or a FSH variant containing an alpha and beta subunit, and a second vial containing phosphate buffer containing saline or a salt.

26. A formulation of Claim 21, wherein said FSH or a FSH variant and said phosphate buffer are in solution.

27. A formulation of Claim 21, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit: (SEQ ID NO:1)

FPDGEPTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKTMLVPKN  
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β-subunit: (SEQ ID NO:2)

RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL  
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFPEIKE

(b): α-subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYIQCKGCCFSRAYPTPARSRKTMVLVPKN  
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β-subunit: (SEQ ID NO:4)

NSCELTNITITAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
VYETVKVPGCAHHADSLYTPVATACHCGKCNDSSTDCTVRGLGPSYCSFGDMKE

- (c):  $\alpha$ -subunit: (SEQ ID NO:5)  
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS  
 $\beta$ -subunit: (SEQ ID NO:6)  
5 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL  
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSDCTVRGLGPSYCSFGEMKE
- (d):  $\alpha$ -subunit: (SEQ ID NO:7)  
FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN  
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS  
10  $\beta$ -subunit: (SEQ ID NO:8)  
NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSDCTVRGLGPSYCSFSEMKE
- (e):  $\alpha$ -subunit: (SEQ ID NO:9)  
FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN  
15 ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS  
 $\beta$ -subunit: (SEQ ID NO:10)  
RSCELTNITITVEKEECSCFISINTTWCAGYCYTRDLVYKDPARPNIQACTFKE  
LVYETVKVPGCAHHADSLYTPVATECHCGKCDSDSDCTVRGLGPSYCSFSDIR  
E
- 20 (f):  $\alpha$ -subunit: (SEQ ID NO:5)  
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS  
 $\beta$ -subunit: (SEQ ID NO:11)  
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL  
25 VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSDCTVRGLGPSYCSFGE
- (g):  $\alpha$ -subunit: (SEQ ID NO:5)  
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS  
 $\beta$ -subunit: (SEQ ID NO:12)  
30 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL  
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSDCTVRGLGPSYCSFGEM
- (h):  $\alpha$ -subunit: (SEQ ID NO:5)  
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS  
35  $\beta$ -subunit: (SEQ ID NO:13)



variant in the aqueous diluent to form a solution that is suitable for use over a period of 24 hours or greater.

36. The article of manufacture of Claim 35, wherein said first vial and said second vial are embodied in a pen-injector device.

37. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, in an aqueous phosphate buffered diluent, said solution being suitable for administration over a period of 24 hours or greater.

38. A method of using a solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant in an aqueous diluent suitable for use over a period of 24 hours or greater.

39. The use of at least one polypeptide of a FSH or a FSH variant in the preparation of a stable formulation adapted for administration over a period of 24 hours or greater.

40. A formulation as described herein.

41. An article of manufacture as described herein

42. A process as described herein.

43. A use as described herein.

44. A method as described herein.

45. Use of a formulation of claim 1 for treating infertility in a patient in need thereof.

46. Use of a formulation of claim 1 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

47. Use of a preserved solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, said solution being suitable for administration over a period of 24 hours or greater.



48. Use of a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of said FSH or a FSH variant in a phosphate buffer, containing saline or a salt, over a period of 24 hours or greater.

49. Use of a formulation of Claim 21 for treating infertility in a patient in need thereof.

50. A use of Claim 49 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

51. Use of a stable solution of purified FSH or a FSH variant, containing an alpha and beta subunit, in a phosphate buffer containing saline or a salt suitable for administration over a period of 24 hours or greater for treating infertility in a patient in need thereof.

52. Use of a stable solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, wherein said stable solution of said FSH or a FSH variant in phosphate buffer containing saline or a salt is suitable for use over a period of 24 hours or greater.

53. A process of producing a formulation comprising admixing a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

54. A process of producing a stable formulation comprising admixing at least a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, and a phosphate buffer containing saline or a salt, wherein

said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

55. A process of Claim 53, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

56. A process according to any of Claims 53-54, wherein the concentration of FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

57. A process according to any of Claims 53-54, further admixing an isotonicity agent.

58. A process of Claim 53-54, further admixing a physiologically acceptable buffer.

59. A process comprising preparing a non-gaseous preparation FSH or a FSH variant lyophilized in a first vial, and preparing a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

60. A process of Claim 59, wherein said FSH or a FSH variant and preservative are further put into solution.

61. A process according to any of claims 53-54, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit: (SEQ ID NO:1)

FPDGEFTMQGCPCKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMVLVPKN  
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β-subunit: (SEQ ID NO:2)

RSCELTNITITVEKEECGFCISINTTWAGYCYTRDLVYRDPARPNIQKTCTFKEL  
VYETVKVPGCAHADSPLYTPVATECHCKSDSDTCTVRLGLGPSYCSFREIKE

(b): α-subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYQCKGCCFSRAYPTPARSRKTMVLVPKN  
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β-subunit: (SEQ ID NO:4)

NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
VYETVKVPGCAHHADSLYTPVATACHCGKCNDSSTDCTVRGLGPSYCSFGDMKE

(c): α-subunit: (SEQ ID NO:5)

5 APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β-subunit: (SEQ ID NO:6)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL  
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

10 (d): α-subunit: (SEQ ID NO:7)

FPDGFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN  
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

β-subunit: (SEQ ID NO:8)

15 NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL  
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e): α-subunit: (SEQ ID NO:9)

FPDGFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN  
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β-subunit: (SEQ ID NO:10)

20 RSCELTNITITVEKEECSCFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL  
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSDIRE

(f): α-subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

25 β-subunit: (SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL  
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFSGE

(g): α-subunit: (SEQ ID NO:5)

30 APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β-subunit: (SEQ ID NO:12)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL  
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h): α-subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE  
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

$\beta$ -subunit: (SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCIFKEL

5

VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK